

POINTS TO CONSIDER

SCIENTIFIC ABSTRACT

Stem cell transplantation can effectively treat a wide variety of malignant diseases, but a shortage of MHC identical related or unrelated donors impedes the broadest application of this therapy. Haploidentical donors can be substituted for MHC identical or unrelated donors, and recent advances in stem cell collection and purification have made this option more attractive. However, while largely overcoming the problems of graft rejection and graft versus host disease (GvHD), this alternative approach has not increased long-term survival. Patients show prolonged delays in immune reconstitution, and there is a devastatingly high rate of lethal infection with opportunistic organisms. Because the frequency of alloreactive cells causing GvHD is so much higher than the frequency of lymphocytes specific for opportunist organisms, it is not possible to safely improve immune reconstitution by infusing recipients with unmodified donor T cells. One alternative is to first deplete donor T cells of alloreactive lymphocytes by destroying or rendering unresponsive any T cell that reacts with recipient leukocytes. There have been encouraging initial results using this approach. We propose to use EBV-transformed patient-derived B cells to allo-activate donor T cells, and use an ablative immunotoxin (RFT5) directed against the T-cell activation antigen CD25 to remove the alloreactive cells capable of producing GVHD. The allodepleted T cells will then be returned to the recipients after stem cell transplantation, using a dose escalation approach. However, since small numbers of donor T cells will have remained in the stem cell graft, and since new T cells may be generated from precursor cells, it is not possible to directly discern whether the infused allodepleted T lymphocytes persist and genuinely contribute to host immune reconstitution, nor to discover if they remain capable of contributing to Graft versus Host Disease. Hence we plan to draw on our extensive experience with retroviral gene marking of T lymphocytes, to track the survival, expansion and function of the infused T cells, enabling us to modify and optimize the allodepletion protocol as necessary. We will use the systems successfully implemented for gene marking of infused (EBV-specific) T cells in our earlier studies of allogeneic transplant patients.